Case No.: HA160a #2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group: 125
Examiner:
Applicant: Horovitz et al.
Serial No.: 958062
Filed: Herewith
For: Method of Treating Hypertension and Medicaments Therefor

Princeton, New Jersey 08540
November 7, 1978

PRIOR ART STATEMENT

This prior art statement is being presented as a means of complying with the requirements of 37 CFR 1.56. The patents and publications listed below are believed by the undersigned to be the closest prior art. However, no representation is made that better art does not exist nor that a search has been made.

The following were submitted in the parent application:

3,081,230	Weinstock et al.	March 12, 1963
3,137,625	Biel	June 16, 1964
4,046,889	Ondetti et al.	Sept. 6, 1977

Physicians Desk Reference, 31 ed. (Medical Economics Co., 1977), pages 507, 517, 534, 902, 1009, 1116, 1235, 1289, 1416, 1442, 1468.

The Weinstock et al. patent relates to a group of 2,4,7-triamino-6-phenylpteridines having anti-aldosterone activity inducing diuresis and/or hypotension.

The Biel patent relates to a composition and method for inducing diuretic activity involving a combination of a thiazide diuretic like chlorothiazide, hydrochlorothiazide and the like with a mercurial diuretic like chlormerodrin or merbiurelidin.

The Ondetti et al. patent discloses mercaptoacyl derivatives of prolines, azetidine-2-carboxylic acids and pipecolic acids including 1-(3-mercapto-2-methylpropanoyl)-L-proline and related compounds useful in relieving angiotensin related hypertension.

The pages cited from Physicians Desk Reference show the following combinations for diuretic/saluretic and/or anti-hypertensive effects:

p. 507	methylclothiazide-deserpedine
517	pargyline HCl-methylclothiazide
534	Hydrochlorothiazide-deserpedine
902	quinethazone-reserpine
1009	methyclothiazide-reserpine
1116	trichlomethiazide-reserpine
1235	polythiazide-reserpine
1289	benzthiazide-reserpine
1416	trichlormethiazide-reserpine
1442	spironolactone-hydrochlorothiazide
1468	triamterene-hydrochlorothiazide

The foregoing are submitted as representative of cumulative disclosures of such combinations.

The Examiner, in addition, cited the following in the parent application:

Chem. Abstr. 85, 1976, p. 41027,

85: 41026m; 82, 1975, pp. 42-43,

82: 11322a

Clin. Sci. and Mol. Med. 48, 53s-56s (1975)

C.A. 82 relates to vasoconstriction with furosemide (administered IV) and lack of reduction of that activity by treatment with SQ20,881, an ACE inhibitor.

C.A. 85 relates to treatment of hypertension with ACE inhibitor SQ20,881 and refers to enhancement of response with diuresis with furosemide.

The Clinical Science article is the complete article abstracted in CA85 and is relied upon to show that SQ20,881 was administered intravenously.

The following are referred to in the specification attached:

Science 196, 441-443 (1977)

Jour. Pharm. Exper. Ther. 204, 271-280, 281-288 (1978)

Brit. Med. Jour. 2(6141):866(1978)

Drugs 14:420-460(1977)

Circ. Res. 43, I-45--I-53(1978)

The Science article is cumulative to U.S. Patent 4,046,889 in showing compounds of formula I. It describes that it was discovered in a search for antihypertensive agents having the activity of the nonapeptide SQ20,881 but overcoming the disadvantage of the latter in lacking oral activity.

The articles in Jour. Pharm. Exper. Ther. are relied on to show that the nonapeptide teprotide (SQ20,881) is not effective when administered orally.

The review article in Drugs is relied upon to show that treatment with an antihypertensive alone results in

compensatory retention of sodium and water.

The article in Circulation Research shows that a compound of formula I alone does not result in sodium and water retention and may cause natriuresis and diuresis.

Copies of all the foregoing are attached.

Respectfully submitted,

Attorney

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